REMARKS

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Claims 1 and 14 have been amended to recite SNPs of Table 1. Support for the amendment can be found at least in paragraph [0043] and Table 1. Claim 14 has been withdrawn in response to a restriction requirement. Applicants specifically reserve the right to pursue the withdrawn subject matter in a continuing application, if the claim is not rejoined later. Claim 15 has been added, support for which can be found in Table 2.

After amending the claims as set forth above, claims 1-7 and 10-13 and 15 will be pending in this application.

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. RESTRICTION

The examiner objects to claim 14 for allegedly being drawn to a nonelected invention. Applicants have withdrawn the claim and, thereby, obviated the rejection.

II. OBJECTION

The examiner objects to claims 1-7 and 10-13 for referencing Table 1. Applicants note that the claims reference Table 1 for three pieces of information: (i) the amino acid positions of X (i.e., positions 2, 3, 4, 19, 37, 40, 49, 67, 78, 82, 90, 102, 113, 122, 125, 127, 143, 151, 161, 162, 163, 180, 182, 194, 202, 216, 235, 236, 237, 241, 258, 261, 264, 271, 272, 276, and 285 of the bla-TEM-1 gene), (2) the wild type TEM-1 sequence at each position and (3) the mutant TEM sequence at each position. Applicants assert that referencing Table 1 for the cited information is the most practical way to define the invention

and is more concise than duplicating the table into the claims. Applicants request, therefore, that the rejection be withdrawn.

III. REJECTIONS UNDER 35 U.S.C. § 112

The examiner rejects claims 1-7 and 10-13 under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement. Applicants respectfully traverse the rejection.

While the examiner acknowledges that the specification enables methods of detecting beta-lactam resistant micro-organisms by employing a micro-array wherein each representative of a set of capture probes comprises the sequence R1-(X)-R2, wherein X consists of the nucleotide triplets of amino acid positions 2, 3, 4, 19, 37, 40, 49, 67, 78, 82, 90, 102, 113, 122, 125, 127, 143, 151, 161, 162, 163, 180, 182, 194, 202, 216, 235, 236, 237, 241, 258, 261, 264, 271, 272, 276, and 285 of the bla-TEM-1 gene, wherein R1 consists of 25 consecutive nucleotides immediately 5' to X, and wherein R2 consists of 25 consecutive nucleotides immediately 3' of X, he asserts that the specification does not enable the use of "any" nucleotide triplet in Table 1 with "any" three nucleotides on either side of the triplet that are specific to any TEM beta lactamase gene. Office Action, pg. 5.

So stating, the examiner overlooks the fact (1) that Table 1 specifically identifies the triplets for wild type and mutant sequences for each residue of interest and (2) that regions R1 and R2 are necessarily adjacent to the triplet X on the TEM beta lactamase. Furthermore, regarding the use of flanking sequences of about 3 to 20 nucleotides, applicants note that selection of probe length is among the most basic skills in designing hybridization reactions. It is not surprising, therefore, that nothing in the record suggests that anything more than routine skill would be required to make and use the claimed arrays.

Nevertheless, applicants have amended the claims to clarify the nature of the triplets shown in Table 1 and of the flanking regions employed by the capture probes in the recited micro-arrays. As one of ordinary skill in the art would be able to readily use, without undue experimentation, the arrays described in Table 1 to detect beta-lactam resistant micro-organisms, the claimed methods are fully enabled under §112. Applicants request, therefore, that the rejection be withdrawn.

The examiner also rejects claims 1-7 and 10-13 under 35 U.S.C. § 112, first paragraph, for an alleged lack of written description. Applicants respectfully traverse the rejection.

According to the examiner, the claims "broadly encompass every sequence in every genome, known or unknown." Office Action, pg. 11. Applicants respectfully disagree. As the sequences concern capture probes, which by definition must hybridize to a target sequence, an artisan reviewing the application would recognize instantly that regions R1 and R2 are necessarily adjacent to the triplet X on the TEM beta lactamase. Nevertheless, applicants have amended the claims to clarify this point and believe the amendments obviate the rejection.

IV. REJECTIONS UNDER 35 U.S.C. § 103

The examiner rejects claims 1-6, 8, 9, 11 and 13 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Lee et al. in view of Balzquez et al., Chee et al (A) (WO 95/11995) and Sutcliffe. Meanwhile, claim 7 is rejected being allegedly unpatentable over Lee, Blazquez, Chee (A) and Sutcliffe, in view of Osano et al. Claim 10 is rejected as being allegedly unpatentable over Lee, Blazquez, Chee (A), and Sutcliffe in view of Chee (B) et al and Routier. Claim 12 is rejected as being allegedly unpatentable over Lee, Balzquez, Chee(A), and Sutcliffe in view of Behrensdorf et al. Applicants respectfully traverse the rejections.

The present methods involve the use micro-arrays with capture probes utilizing the 44 triplets provided in table 1 and their mutant counterparts for the specific detection of the beta-lactamases TEM, ESBL and IRT phenotypes. The flanking regions of the capture probes comprise sequences of between 3 and 20 nucleotides that are adjacent to the relevant triplet on the TEM enzyme. In another aspect, the claimed methods employ a micro-array comprising the capture probes disclosed in Table 2 (*i.e.*, SEQ ID NOS: 5 to 45). Thus, the inventive methods provide a practitioner, in a single assay, with a complete picture of a patient's status as to beta-lactam resistant microorganisms. Such assays represent a significant advancement in patient care that is neither taught nor suggested by the prior art.

The examiner cites Lee for disclosing a micro-array for the detection of various beta-lactamase resistant genes. Blazquez is cited for teaching that amino acid replacement at seven residues of the TEM1 gene can alter resistance of microorganisms to specific antibiotics. Meanwhile, Chee (A) is cited for teaching a tilling array, and Sutcliffe is cited for disclosing the nucleotide sequence of the beta-lactamase gene. Osana is cited for teaching that class A and C beta-lactamases are serine dependent, that class B beta-lactamases are zinc-dependent and that some strains of the Enterobacteriaceae family are resistant to imipenem therapy. Chee (B) is cited for teaching that fragmentation improves uniformity and specificity of hybridization, while Routier is cited for teaching a method of fragmentation. Behrensdorf is cited for allegedly teaching the detection of SNPs by binding fluorescently labeled mutS to mismatched DNA.

The cited materials, however, do not teach or suggest the use micro-arrays with capture probes utilizing the 44 triplets provided in table 1 and their mutant counterparts for the specific detection of the beta-lactamases TEM, ESBL and IRT phenotypes. Likewise, the cited portions do not foretell the use of a micro-array comprising capture probes having the nucleic acid sequences of SEQ ID NOS: 5 to 45. Similarly, the cited materials fail to disclose or suggest using sets of such capture probes in a method for detecting the presence of a beta-lactam resistant micro-organism in a biological sample and simultaneously determining the genotype of the beta-lactam resistance. Thus, no combination of the cited references presages the claimed invention.

In addition, the examiner has not shown the apparent reason to combine the various elements in the cited art in the fashion claimed, with the requisite expectation of success that the Supreme Court recently explained is required to establish obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740-1741 (2007). In applying *KSR*, the Federal Circuit has found non-obviousness where the claims were directed to a specific chemical compound and "the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." *Takeda Chem. Industs., Ltd. v. Alphapharm Pty, Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007); *See also Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358 (Fed. Cir. 2008).

As in the *Takeda* case, the cited references here disclose a number of possible steps but provide no reason for selecting the particular combination of Applicants' claimed methodology. For example, the cited references concern basic methodology for employing arrays and provide general information concerning beta-lactamase. Yet, nothing in the cited material would have guided an artisan contemplating a method for detecting the presence of a beta-lactam resistant micro-organism in a biological sample and simultaneously determining the genotype of the beta-lactam resistance to a method specifically employing the arrays as claimed.

Thus, a *prima facie* case obviousness has not been established. Applicants request, therefore, that the rejection be withdrawn.

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Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extension of time is needed for timely acceptance of papers submitted herewith, applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extension fee to Deposit Account No. 19-0741.

Respectfully submitted,

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